DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

DEC 6 2006

By Certified Mail – Return Receipt Requested
And by Facsimile Transmission

CBER- 07-004

Warning Letter

Mary Pat Moyer, Ph.D., President
INCELL Corporation, LLC
12000 Network Boulevard, Suite B-200
San Antonio, Texas 78249

Dear Dr. Moyer:

This letter describes the results of a Food and Drug Administration (FDA) inspection that concluded on September 19, 2006. FDA Investigator Joel Martinez met with you to review INCELL Corporation's conduct of studies performed under the Good Laboratory Practices (GLP) regulations [Title 21, Code of Federal Regulations, (CFR) Part 58]. The inspection was conducted as part of FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational drugs.

At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you and your staff. We received and reviewed your October 20, 2006 letter responding to the Form FDA 483 issued at the close of the inspection.

Based on the information obtained during the inspection, we conclude that INCELL Corporation, LLC (INCELL) has violated GLP regulations governing the proper conduct of nonclinical studies as published under 21 CFR Part 58. The applicable provisions of the CFR are cited for each violation.

1. **INCELL failed to establish a Quality Assurance Unit responsible for monitoring each study. [21 CFR § 58.35].**

   At the time of the inspection, INCELL had not established a quality assurance unit (QAU), in violation of the regulation. As a result, a QAU failed to perform the following required duties, among others: a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility was not maintained, copies of protocols pertaining to nonclinical laboratory studies were not maintained, inspections of each nonclinical laboratory study at adequate intervals to assure the integrity of the study were not conducted, and final study reports were not reviewed by a QAU. [21 CFR § 58.35 (b)(1), (2), (3), (6)]

In your letter, you indicate that you plan [redacted] as soon as possible. In the interim period, you have designated a current employee to assume QAU duties.

2. **INCELL failed to maintain complete protocols for nonclinical laboratory studies. [21 CFR § 58.120].**

Records of study protocols reviewed during the inspection failed to include the date of approval by the sponsor, a description of the animal diet, or a description of study records to be maintained. [21 CFR § 58.120(a)(7), (10), (11)]

According to your response letter, you have revised study protocol forms and formats to include this information.

3. **INCELL failed to prepare adequate reports of nonclinical laboratory study results. [21 CFR § 58.185].**

A. The final study reports for the [redacted] are deficient in that they failed to include: the name of the study director; the storage location for specimens, raw data, and the final study report; a QAU statement prepared under 21 CFR § 58.185(a)(14); the signature of the study director; and the date the study director signed the report. [21 CFR §§ 58.185(a)(10), (13), (14); 58.185 (b)]

B. Section 5.4, "Summary of Results" of the Test Report Form, represented by Incell as the form for final study reports, is incomplete because it lacks a description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis. [21 CFR § 58.185(a)(11)] The investigator found incomplete final study reports for the following studies: [redacted]

C. Final study reports for the following studies were not adequate because they did not include information about [redacted] that died during the study.

Study	# of Dead	Not Reported in Results	Date
[redacted]	3	[redacted]	12/09/05
	5		12/10/05
	2		12/11/05
[redacted]	2		09/16/05
	3		09/18/05
	1		09/20/05
[redacted]	4		08/06/04
	6		08/07/04
[redacted]	1		08/06/04

Your response states that you have redesigned forms, including revision of your final report template, and implemented new staff training programs to assure study reports are complete and have proper QAU oversight. You have designated the study director as responsible for completing the summary section as well as other parts of the Final Study Report, including the documentation of animals found dead during the study. The QAU will review the Final Study Report and ensure completeness and accuracy.

4. **INCELL failed to prepare required written standard operating procedures (SOP). [21 CFR § 58.81].**

A. At the time of inspection, INCELL did not have an SOP for the handling of animals found dead or moribund during nonclinical laboratory studies. [21 CFR § 58.81(b)(6)]

In your response, you state a "written SOP for handling animals found morbid or dead during the study is attached." The attachment provides information regarding dead animals specific to the studies reviewed during the inspection. However, the attachment did not include an SOP to be followed. Your response further states "A written SOP on the handling of moribund or dead animals will be included in future Study protocols." Although information regarding the handling of animals found dead or moribund during the study can be included with the protocol, the regulation requires that INCELL management establish an INCELL SOP regarding the handling of dead or moribund animals applicable for all nonclinical laboratory studies conducted by INCELL.

In your reply to this letter, please submit a copy of INCELL's procedure for handling of animals found dead or moribund during nonclinical laboratory studies.

B. At the time of inspection, INCELL did not have an SOP for the maintenance and calibration of the [redacted] reader. [21 CFR § 58.81(b)(11)]

In your response, you state you will maintain adequate records for equipment used in GLP studies including maintenance SOPs.

5. **INCELL failed to adequately characterize the test and control article. [21 CFR § 58.105].**

Reserve samples from each batch of test article were not retained for studies longer than 4 weeks. [21 CFR § 58.105(d)]

Your letter states that the Study Director and the QAU will ensure that each study longer than four weeks will require preparation of excess test article and retention of adequate amounts of reserve sample.

6. **INCELL failed to adequately maintain and calibrate equipment used to generate, measure, or assess data in nonclinical laboratory studies. [21 CFR § 58.63(a)].**

The [redacted] reader used to generate stability data requires periodic quality control tests of linearity and precision. These tests have not been performed and an appropriate interval for the performance of these tests has not been established to assure acceptable performance of the [redacted] reader.

Your response states you will maintain adequate records for equipment used in GLP studies including maintenance SOPs, maintenance records, and up-to-date calibration records clearly indicating the test dates and results of the tests.

7. **INCELL failed to maintain archives for storage and retrieval of data. [21 CFR § 58.190(b)].**

The inspection found that archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports were not maintained. Data was not retrievable showing the cell line and/or lot number of the test article used in studies [redacted], and [redacted] In addition, documentation was not retrievable for [redacted] stability testing at [redacted] and [redacted] weeks at [redacted] and [redacted] C.

You attached general information and raw data about these studies to your response. You state there will be more details to follow regarding the [redacted] and [redacted] study documentation.

We further recommend that INCELL develop a procedure for storage and expedient retrieval of study records and data.

We also note that test article accountability records are deficient in that measures were not taken to ensure accurate administration of the test article. As an example, the [redacted] preparation records for study [redacted] document the preparation of [redacted] doses of the [redacted] oral [redacted] formulation. All [redacted] doses were [redacted] and the doses were administered to [redacted] for a total of [redacted] doses. The quantity remaining in the syringe was not measured to ensure that the proper dose of the test article was administered and the quantity remaining was not recorded.

cc: Michael Chappell, District Director

In your letter you explain that as part of the revised documentation and compliance procedures, record keeping will include precise tracking of the test article and control article preparation, dosing, total usage, and remaining material.

The deviations listed above are not intended to be an all-inclusive list of GLP deficiencies that may exist at your testing facility. As a GLP testing facility, you are responsible for ensuring that you conduct nonclinical studies according to FDA regulations.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that failure to implement effective corrective actions and/or the commission of further violations may result in the FDA taking regulatory action without further notice.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future nonclinical studies. Please include INCELL's SOP for handling of animals found dead or moribund during nonclinical laboratory studies with your submission.

Please send your written documentation to:

Christine J. Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6323

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Michael Chappell, District Director
Food and Drug Administration
4040 North Central Expressway, Suite 300
Dallas, Texas 75204